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Controversy

Is there a relation between type of primary melanoma treatment and the development of intralymphatic metastasis? A review of the literature ☆

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ABSTRACT

Background: Intralymphatic metastases (ILM) originate from tumor cell emboli entrapped in dermal lymphatics between primary tumor and regional lymph node basin. Because of this origin, sentinel lymph node biopsy (SLNB) might increase ILM by restricting lymph flow.
Methods: Pubmed, Embase, Cochrane and Medline were searched for articles on ILM between 1980 and September 2014. ILM Incidences were calculated after wide local excision (WLE), excision with elective lymph node dissection (ELND) or therapeutic lymph node dissection (TLND), WLE with SLNB with or without completion lymph node dissection (CLND) and delayed lymph node dissection (DLND) for patients developing nodal metastasis during follow-up.
Results: In 36 studies, 14,729 patients underwent WLE, 1682 patients WLE/ELND, 362 patients WLE/DLND and 11,201 patients WLE/SLNB. On meta-analysis, ILM occurrence was 3.4% (95% CI 2.8–4.2%). ILM occurred most frequently in the WLE/DLND group (5.5%, 95% CI 3.5–8.7%), followed by WLE/ELND (4.7%, 95% CI 3.1–7.0%), WLE/SLNB (4.5%, 95% CI 3.5–5.7%) and WLE alone (1.9%, 95% CI 1.4–2.7%). 1330 SLNB+ patients were identified and 5783 SLNB− patients. For these groups, on meta-analysis, ILM recurrence was 13.2% (95% CI 10.8–16.2%) and 3.4% (95% CI 2.5–4.5%), respectively ($p = 0.01$).
Conclusion: In this review SLNB is associated with an increase of ILM with an incidence of 1.9% for WLE vs. 3.4% for SNLB−. Selection bias in this review cannot be excluded. However, ILM occur four times more frequently after SLNB+ than SLNB− procedures and more often after SLNB+/CLND than WLE/DLND or WLE/ELND. ILM should therefore be viewed as a bio-marker of aggressive primary disease.
Synopsis: Sentinel lymph node biopsy is thought to increase intralymphatic metastasis by restricting lymph flow. This review demonstrates that there is an increase in metastasis, but this result has to be interpreted with caution due to possible selection bias. Aggressive tumor characteristics are likely the cause of this increase.

Introduction

The behavior of cutaneous melanoma is notoriously unpredictable. 5-year survival rates deteriorate as stage progresses. For stage IA, IB, IIA, IIB, and IIC these survival rates are 97%, 92%, 81%, 70% and 53%, respectively. 5-year survival for locoregional metastasis is 78% (stage IIIA), 59% (stage IIIB) and 40% (stage IIIC) [1]. Once melanoma has metastasized distantly survival is around 15–20%, although these rates are expected to improve upon the recent introduction of BRAF targeted drugs, checkpoint inhibitors and new generation immunotherapies [2–9]. Long-term follow-up reveals that ulceration and sentinel lymph node status are the strongest predictors for survival [10,11].

The concept of incidence of locoregional metastases increasing with tumor thickness was recognized decades ago [12–14]. Previously, in transit metastases (ITM) and satellite lesions (SL) were considered different entities, but The American Joint Committee on Cancer (AJCC) has classified both ITM and SL in 2002 as intralymphatic metastases (ILM) [15]. Historically, SL have been defined to reside within centimeters of the primary tumor location and ITM in the pathway between primary site and regional lymph node basin. The leading hypothesis is that both originate from tumor cell emboli entrapped in dermal lymphatic vessels between primary tumor and regional lymph node basin [16,17]. The appearance of

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ILM automatically upstages a patient's disease into stage IIIB/IIIC, decreasing 5-year survival to 59% and 40%, respectively [1]. Survival rates for patients with SL alone, SL/ITM, or ITM are identical and similar to that of patients with nodal disease [18]. Scar recurrence, 'true local recurrence', differs in pathophysiology, as these develop from residual cells of the initial melanoma, a result of false-negative margins or microsatellites.

Curative treatment for primary melanoma remains surgery (wide local excision, WLE) [2,19]. Four prospective additional elective lymph node dissection (ELND) trials showed no impact on survival [20–24]. ELND has become redundant after the introduction of the sentinel lymph node biopsy (SLNB) in 1992, which preserves its diagnostic advantage with less morbidity [21–23,25–27]. Patients with a positive SLNB undergo a completion node dissection (CLND). The MSLT-I study showed a small but significant disease-free and melanoma-specific survival benefit in patients with intermediate thickness melanoma (1.2–3.5 mm) and nodal disease following early treatment [28]. Most notably, a melanoma-specific survival improvement of 20% was reported for patients with intermediate thickness melanoma undergoing SLNB as opposed to observation, although the MSLT-I did not show improvement in recurrence free, distant metastasis free and melanoma specific survival for the entire population. The MSLT-II study will answer in the near future whether a CLND is indeed indicated after a positive SLNB [29,30]. Other treatment modalities have included therapeutic lymph node dissection (TLND), for metastatic nodal disease at the time of diagnosis, and delayed lymph node dissection (DLND), for patients developing metastatic nodal disease [31].

SLNB in addition to WLE alone has been suspected of causing ILM by inducing lymphatic stasis or entrapment of melanoma cells [32,33]. Pathophysiology on which this hypothesis is built is that the lymph flow from the skin reaches the nodal basin within minutes, with melanoma cells still in lymphatic channels *en route* to the lymph node basin at the time of SLNB or nodal dissection [33,34]. Estourgie et al. published a fourfold risk of ITM recurrence in SLNB positive patients as compared to SLNB negative patients, thereby raising the question whether surgical treatment of the regional lymph node basin can be responsible for ITM, although the same research group refuted this finding in a larger population [35,36]. Although various authors have studied this phenomenon, most notably Morton et al. in the aforementioned MSLT-I trial and van Poll et al. using data of the Melanoma Institute Australia, a definite answer as to whether the incidence of ILM should be attributed to unfavorable primary tumor characteristics alone or is increased by the SLNB procedure by means of a review of all available data has not yet been published [10,16,28,37,38].

The objective of this review was to provide an extensive body of evidence, answering the question whether ILM frequencies increase after performing SLNB.

Methods

Pubmed, Embase, Cochrane Library and Medline were searched for articles using the terms 'melanoma' and 'recurrence' or 'in transit metastasis' or 'ITM' or 'SL' or 'intralymphatic metastasis' or 'local recurrence' or 'satellite' or 'sentinel node' or 'survival' between January 1980 and September 2014. Articles were excluded if they had not been written in English, if they did not distinguish between a local recurrence and ILM, if incidence for ILM as a first recurrence (FR) was not reported, if studies exclusively reported on SLNB− or SLNB+ or if treatment strategy was unclear. Duplicates, case reports, letters to the editors and case series were excluded. Data regarding ILM as FR derived from our institution's SLNB database (UMCG database) were added to the review.

ITM was classified as recurrent melanoma in the pathway between primary melanoma location and the regional nodal basin, with the lesion more than two or five centimeters from this location, depending on the definition used in the article. All other cutaneous and subcutaneous metastases between the re-excision scar and the location of ITM were classified as SL. As consensus is now that ITM and SL are the same entity, all ITM and SL were combined into one value, 'ILM'.

For all included articles the number of patients with ILM as first recurrence (FR) were calculated per treatment group: for WLE alone, for WLE with ELND, WLE and DLND or TLND and WLE with SLNB. The last group was stratified into tumor-negative SLNB (SLNB−) patients and tumor-positive SLNB (SLNB+) patients undergoing CLND. When assessing risk of ILM as FR, WLE was compared to the WLE/SLNB− group. WLE/SLNB+ was compared to WLE/DLND, WLE/ELND and WLE/TLND groups. As only SLNB+ patients undergo additional CLND, this division groups together the most similar procedures regarding interruption of lymph flow. Additional study characteristics were collected: study design, number of patients, mean/median Breslow thickness, age at diagnosis, and melanoma ulceration status.

Statistical analysis

For a comprehensive review of the data, all data were summarized in tables and analyzed using version 18 SPSS, (IBM, Chicago, Illinois, USA). Descriptive statistics were used to calculate frequencies of ILM for the different treatment strategies. Chi-square tests were used to check for significant differences.

Subsequently, all studies were assigned a weight based on the amount of included patients and entered into a meta-analysis. Meta-analyses were performed stratified for treatment, SLNB results and anatomical localization of the primary tumor. Proportions of ILM and the corresponding 95% CI were calculated and entered in a datasheet. Meta-analyses were performed with the 'metan' module using STATA/SE version 12.0 (StataCorp, College Station, Texas, USA) with the original data as reported in the studies. Pooled ILM proportions and their 95% CI were calculated using a random effects model.

Results

Study characteristics

19,620 studies were identified and assessed according to the inclusion criteria. 36 studies with a total of 33,622 patients were included for analysis (Table 1), including our ongoing academic medical center database (UMCG database). 6 studies were excluded because they exclusively reported on SLNB− or exclusively on SLNB+ patients ($n = 684$ patients) [11,39–43]. Median follow-up ranged from >12 months–11 years. Fifteen out of 36 studies reported mean Breslow depth and 6 reported exclusively median Breslow depth. One study reported Breslow depth using incremental depths [44]. Melanoma ulceration status was reported in 23 studies; in 15 of those data were only available for part of the population. Twelve studies provided treatment/recurrence data on WLE (14,729 patients), 5 on WLE/ELND (1682 patients), 1 on WLE/DLND (362 patients) and 18 on WLE/SLNB (11,201 patients). For the remaining 5648 patients in 7 studies, treatment was not specified. No study reported outcomes exclusively for TLND.

In 23 of the 36 included studies a clear definition of ITM/SL was not provided. ITM was defined as (sub)cutaneous disease recurrence between locoregional lymph node basin and 2, 3 or 5 centimeters from the original scar in $n = 5$, $n = 1$ and $n = 4$ studies, respectively. The remaining 3 studies defined ILM as recurrence

Table 1
Characteristics of included studies.

No.	Author	Year	No. patients	Age	Follow-up (median)	Breslow (mm, mean)	Ulceration	No. of ILM	% ILM	No. SLNB patients	SN+		SN−	
											Pts	ILM	Pts	ILM
1	Bagley [12]	1981	103	NR	>5 years (mean	NR	NR	5	4.9	NR	N/A	N/A	N/A	N/A
2	Janoff [14]	1982	122	NR	6.1 years (mean)	NR	NR	8	6.6	NR	N/A	N/A	N/A	N/A
3	Roses [13]	1983	658	NR	44.8 months (mean)	NR	NR	15	2.3	NR	N/A	N/A	N/A	N/A
4	Veronesi [59]	1991	612	0–20: 6 21–40: 217 41–50: 159 51–65: 230	90 months (mean)	1.0	NR	4	0.65	NR	N/A	N/A	N/A	N/A
5	Heenan [45]	1992	482	NR	5 years (mean)	NR	NR	7	0.62	NR	N/A	N/A	N/A	N/A
6	Gadd [60]	1992	1019	56	NR	NR	NR	89	8.7	NR	N/A	N/A	N/A	N/A
7	Fusi [44]	1993	1090	NR	84 months	<0.75 6% <2.25 38% >2.25 56%	NR	20	1.8	NR	N/A	N/A	N/A	N/A
8	Martini [61]	1994	840	53.5	48 months	2.3	NR	24	2.9	NR	N/A	N/A	N/A	N/A
9	Karakousis [62]	1996	742	48.9	92 months (mean)	2.0	Present in 25% NR 17	47	6.3	NR	N/A	N/A	N/A	N/A
10	Johnson [63]	1999	306	50.6	85 months (mean)	NR	NR	1	0.3	NR	N/A	N/A	N/A	N/A
11	Borgstein [16]	1999	258	NR	27 months	1.5 (median)	NR	15	4.3	258	53	N/A	205	N/A
12	Cohn-Cedermark [46]	1999	2493	NR*	11 years	1.1–2.7 (median)**	NR*	49	1.97	NR	N/A	N/A	N/A	N/A
13	Cohn-Cedermark [64]	2000	989	51-52 (median)	11 years	1.2 (median)	NR	9	0.9	NR	N/A	N/A	N/A	N/A
14	Chao [65]	2002	1183	52.0	16 months	NR	Present in 30% NR 56	14	1.2	NR	N/A	N/A	N/A	N/A
15	Goydos [66]	2003	175	NR	NR	NR	NR	14	8.0	175	102	14	73	0
16	Estourgie [35]	2003	250	NR	72 months	2.7	Present in 32% NR 3	32	10.8	250	60	14	190	18
17	Borgognoni [67]	2004	375	55.3	35 months	NR	NR	7	1.9	375	75	1	300	6
18	Macripo [68]	2004	274	51 (median)	2.9 years	1.9 (median)	Present in 8%	10	3.65	274	46	2	228	8
19	Thomas [69]	2004	900	57-58	60 months	3.1 (median)	Present in 33% NR 125	17	1.9	NR	N/A	N/A	N/A	N/A
20	Berk [70]	2005	260	55	29 months	2.3	Present in 25% NR 33	3	1.15	260	39	1	221	2
21	Duprat [71]	2005	240	51 (median)	27.8 months	1.6 (median)	Present in 30%	10	4.17	240	42	N/A	198	N/A
22	Nathansohn [72]	2005	141	53	41 months	NR	Present in 26% NR 30	9	6.4	NR	N/A	N/A	N/A	N/A
23	Kang [20]	2005	4412	NR	NR	NR	Present in 9% NR 45.9%	77	1.7	1016	110	9	906	28
24	Van Poll [47]	2005	2018	57	44 months (mean)	2.4	Present in 26% NR 258	54	2.7	754	102	7	652	11
25	Pawlik [10]	2005	1395	51	46.8 months	1.5 (median)	Present in 21%	86	4.9	1395	234	28†	1136	40
26	Van Akkooi [73]	2006	262	NR	23.3 months	2.8	Present in 28%	11	4.2	262	77	7	185	4
27	Cecchi [74]	2006	111	53 (median)	31.5 months	NR	Present in 32% NR 1	4	3.6	111	17	3	94	1
28	Kretschmer [75]	2006	328	60 (median)	40 months	2.7	Present in 34% NR 16	25	7.6	NR	N/A	N/A	N/A	N/A
29	Dalal [76]	2007	1046	56 (median)	36 months (mean)	2.5	Present in 28% NR 142	50	4.8	1046	163	23	883	27
30	Roulin [77]	2008	327	54	33 months	2.2	Present in 27%	20	6.1	327	74	10	253	10
31	UMCG database	2013	589	53	64.6 months	3.0	Present in 35% NR 10	45	6.1	588	177	30	411	15
32	v/d Broek [78]	2013	305	51	>12 months	1.6	Present in 15% NR 20	10	3.3	305	54	4	251	6

33	Ribero [79]	2013	1693	55.3–57.8 (median)[**]	4.8 years	1.4–2.2[**]	Present in 82%	92	5.4	656	NR	NR	NR	NR
34	Spillane [49]	2014	1704	<50,632 >50 1072	69 months	NR	Yes 549 No 826 Unkn 329	127	7.5	NR	NR	NR	NR	NR
35	Martin [50]	2014	80	49.9–50.9[**]	19.1–33.9 months[**]	2.9–3.1[**]	Present in 53%	12	15	NR	NR	NR	NR	NR
36	v/d Ploeg [80]	2014	5840	56.1–60.2[**]	42 months	2.4–2.5[**]	Present in 25% NR 781	146	2.5	2909	394	NR	2515	NR

Age and Breslow depth are given as means unless otherwise reported. NR = not reported, classified as number of patients. ILM = intralymphatic metastases.

[*] Data incomplete.

[**] Values separately given for two different patient groups.

[†] SLNB status was split out for 68/86 ILM patients.

within the pathway of lymphatic drainage, between scar and regional nodal basin, and between tumor and nodes, respectively. Seven out of 36 studies distinguished SL from ITM; out of these, 2 studies defined SL and LR as the same entity [13,16,35,45–48].

ILM data review

ILM occurred most frequently in the WLE/DLND group (20/362 patients, 5.5%), followed by WLE/ELND (75/1682 patients, 4.5%), WLE/SLNB (both SLNB+ and SLNB−) (474/11,201 patients, 4.2%), and WLE alone (285/14,729 patients, 1.9%). For the remaining 5648 patients, the occurrence of ILM was not specified according to treatment method. This group includes Spillane et al. and Martin et al, who did provide the amount of patients undergoing SLNB, but did not differentiate recurrence rates for CLND/DLND/TLND and CLND/TLND, respectively [49,50] (Table 2).

Of the 11,201 patients undergoing SLNB, ILM was split out according to tumor status in 6913 patients. Of the SLNB+ group 153/1330 patients (11.5%) developed an ILM as FR versus 176/5783 patients (3.0%) in the SLNB− group. Differences in distribution between the four treatment modalities and differences between SN− and SN+ were statistically significant. ILM as FR after WLE was significantly lower than after WLE/SLNB, WLE/ELND and WLE/DLND (all $p < 0.001$). ILM was significantly lower after WLE/SLNB− compared to WLE/SLNB+ ($p < 0.001$) (Table 3).

Meta-analysis

After review of the data a meta-analysis was performed, with weight assigned to studies based on the amount of included patients. The overall ILM incidence was 3.4% (95% CI 2.8–4.2%). In the meta-analysis, outcomes were similar to the review data with ILM occurring most frequently in the WLE/DLND group (5.5%, 95% CI 3.5–8.7%), followed by WLE/ELND (4.7%, 95% CI 3.1–7.0%), WLE/SLNB (both SLNB+ and SLNB−) (4.5%, 95% CI 3.5–5.7%) and WLE alone (1.9%, 95% CI 1.4–2.7%) (Table 3 and Fig. 1). Of the 11,201 patients undergoing SLNB, ILM was split out according to tumor status in 6913 patients. For the 6913 patients whose SLNB outcome status was reported, ILM recurrence was higher than for the 11,201 patients, i.e. 5.8% (95% CI 4.1–8.3%). For SLNB+ patients, ILM occurrence was higher (13.2%, 95% CI 10.8–16.22%) than for SLNB− patients (3.4%, 95% CI 2.5–4.5%) (Fig. 2).

The WLE group had significantly less ILM recurrence than the SLNB group ($p = 0.02$), but not than WLE/ELND and WLE/DLND ($p = 0.21$ and $p = 0.49$, respectively). SLNB− patients had less recurrence than SLNB+ patients ($p = 0.01$) (Table 3).

Discussion

Background

In this review, 33,622 melanoma patients from 36 studies were analyzed to establish whether performing SLNB on melanoma patients in addition to WLE alone leads to an increase in ILM. This is an ongoing field of discussion in the literature. In fact, Read et al. recently published one of the largest databases so far, ($n = 11,614$) where 505 patients developed ILM as a recurrence at any time during follow-up [51]. ILM percentages were 4.7% and 21.6% for SLNB− and SLNB+ patients, respectively. Numbers were not specified for the 190 patients who developed ILM as FR, which explains partly why the numbers are higher than in our study.

Critics of SLNB have argued that as of yet there is no agreement on adjuvant therapy for node-positive patients and that only 20% of the patients undergoing SLNB will have a positive node [52]. However, nowadays there are new approaches available with tar-

geted and/or immunotherapies that may lead to new adjuvant strategies [53,54]. The argument that no randomized controlled studies have shown a survival advantage for SLNB in node-positive patients has become partly redundant upon publication of the MSLT-I, which shows a (small, but significant) survival advantage for a selective group of patients, i.e. patients with an intermediate thickness melanoma and positive SLNB. Proponents advocate that SLNB is a procedure with a relatively low morbidity and that the current false-negative rate for SLNB performed in reputable institutes is <6%, declining further as experience progresses [55,56].

Results

Based on the results of our meta-analysis, the overall incidence of ILM as FR was 3.4%. Patients who did not undergo any lymph node dissection had the lowest incidence, with 1.9% of patients having ILM recurrence after WLE and 3.4% after SLNB−. ILM occurrence after WLE/DLND and WLE/ELND was slightly higher (4.7% and 5.5%, respectively), but incidence spiked after SLNB+/CLND at 13.2%. For TLND, insufficient data were available.

Differences in ILM occurrence between WLE and WLE/SLNB groups were statistically significant, leading to the conclusion that

Table 2
Reviews classified by treatment, sorted by Breslow thickness for available studies.

Author	Year	No. patients	No. of ILM	Percentage ILM	Breslow (mm)
WLE (n = 7308)					
Veronesi [59]	1991	612	4	0.65	1.0 mean
Van Poll [47]	2005	1035	26	2.51	1.8 mean
Martini [61]	1994	840	24	2.85	2.3 mean
v/d Ploeg [80]	2014	2931	51	1.74	2.3* mean
UMCG database [48]	2013	1	0	0.00	3.0 mean
Cohn-Cedermark [64]	2000	989	9	0.91	1.2 (median)
Thomas [69]	2004	900	17	1.89	3.1 (median)
WLE + ELND (n = 609)					
Karakousis [62]	1996	380	27	7.11	2.0 mean
Van Poll [47]	2005	229	10	4.37	3.2 mean
WLE + DLND (n = 362)					
Karakousis [62]	1996	362	20	5.52	2.0 mean
WLE + SLNB (n = 8868)					
v/d Broek [78]	2012	305	6	2.0	1.6 mean
Van Poll [47]	2005	754	18	2.39	1.9 mean
Roulin [77]	2008	327	20	6.12	2.2 mean
Berk [70]	2005	260	3	1.15	2.3 mean
Dalal [76]	2007	1046	50	4.78	2.5 mean
v/d Ploeg [80]	2014	2909	95	3.27	2.5* mean
Estourgie [35]	2003	250	27	10.80	2.7 mean
Van Akkooi [73]	2006	262	11	4.20	2.8 mean
UMCG database	2013	588	45	7.65	3.0 mean
Duprat [71]	2005	240	10	4.17	1.6 (median)
Pawlik [10]	2005	1395	86	6.16	1.5 (median)
Borgstein [16]	1999	258	11	4.26	1.5 (median)
Macripo [68]	2004	274	10	3.65	1.9 (median)

NR = not reported, classified as number of patients. ILM = intralymphatic metastases.
* Separate values given for separate treatment groups.

Table 3
Pooled values and total number of ILM in the treatment groups.

Treatment[a]	Pooled value from meta-analyses		
	Estimate	95% CI	*p*-value
WLE	1.92	1.39–2.66	Reference value
WLE + ELND	4.67	3.10–7.04	0.21
WLE + DLND	5.52	3.50–8.70	0.49
WLE + SLNB	4.46	3.51–5.67	0.02
SN−	3.35	2.52–4.46	Reference value
SN+	13.24	10.80–16.22	0.01

Treatment[b]	Number of ILM			*p*-value
	Total	ILM (%)	No ILM (%)	
WLE	14,729	285 (1.9)	14,444 (98.1)	
WLE + ELND	1682	75 (4.5)	1607 (95.5)	
WLE + DLND	362	20 (5.5)	342 (94.5)	
WLE + SLNB	11,201	474 (4.2)	10,727 (95.8)	*p*-value four groups: <0.001
SN−	5783	176 (3.0)	5607 (97.0)	
SN+	1330	153 (11.5)	1177 (88.5)	SN− and SN+: $p < 0.001$

[a] Pooled estimates from the meta-analyses, according to treatment as shown in Figs. 1 and 2.
[b] Total number of ILM in the treatment groups for the initial treatments and stratified for SN− and SN+, review data. *P*-value for differences in distribution (Chi2).

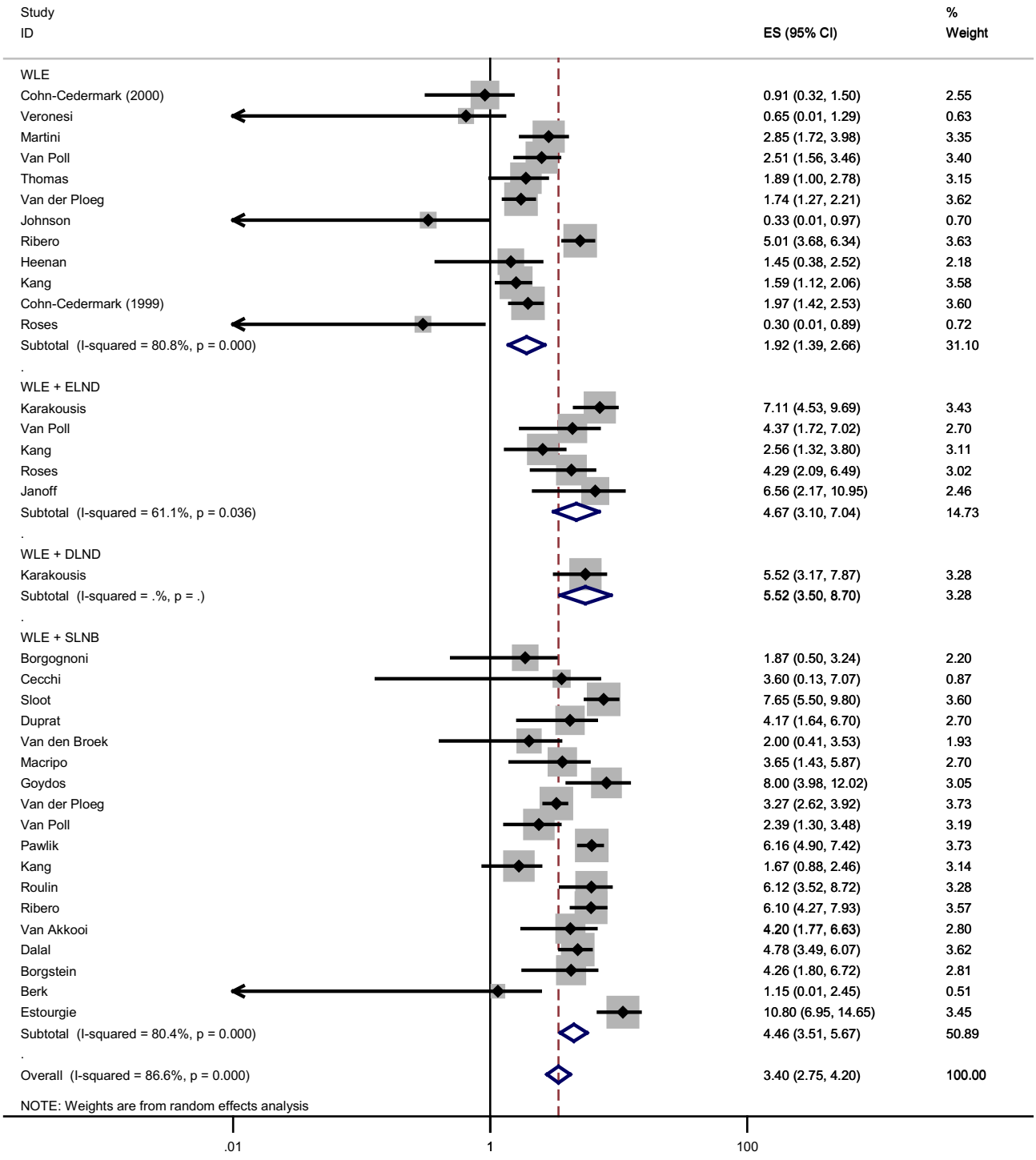

Fig. 1. Pooled percentage of ILM according to treatment.

a sentinel lymph node biopsy alone is associated with an increase in the risk of ILM (from 1.9% to 3.4%, $p = 0.01$).

To test the stasis hypothesis, the most comparable treatment modalities regarding lymph flow disruption are WLE vs. WLE/SLNB− and WLE/SLNB+/CLND vs. WLE/ELND. As metastasis already has occurred in WLE/DLND groups, this is not a good comparator. As ILM incidence according to meta-analysis doubled between WLE vs. WLE/SLNB− and increased almost threefold from 4.7% to 13.2% between WLE/ELND and WLE/SLNB+/CLND groups, ($p < 0.001$), the increase of ILM is unlikely to be due to the increase in lymph stasis. CLND and ELND are comparable in their amount of lymph flow disruption. This suggests that an aggressive tumor behavior is the main reason for ILM, a statement that is supported by the spike in incidence after SLNB+, which is the patient group with the most aggressive tumor biology.

Limitations

Inevitable to any review, authors use different definitions and inclusion criteria. The level of heterogeneity is considerable, as illustrated in Table 1, where data on patient and tumor characteristics are shown. The inconsistent and varied application of terms

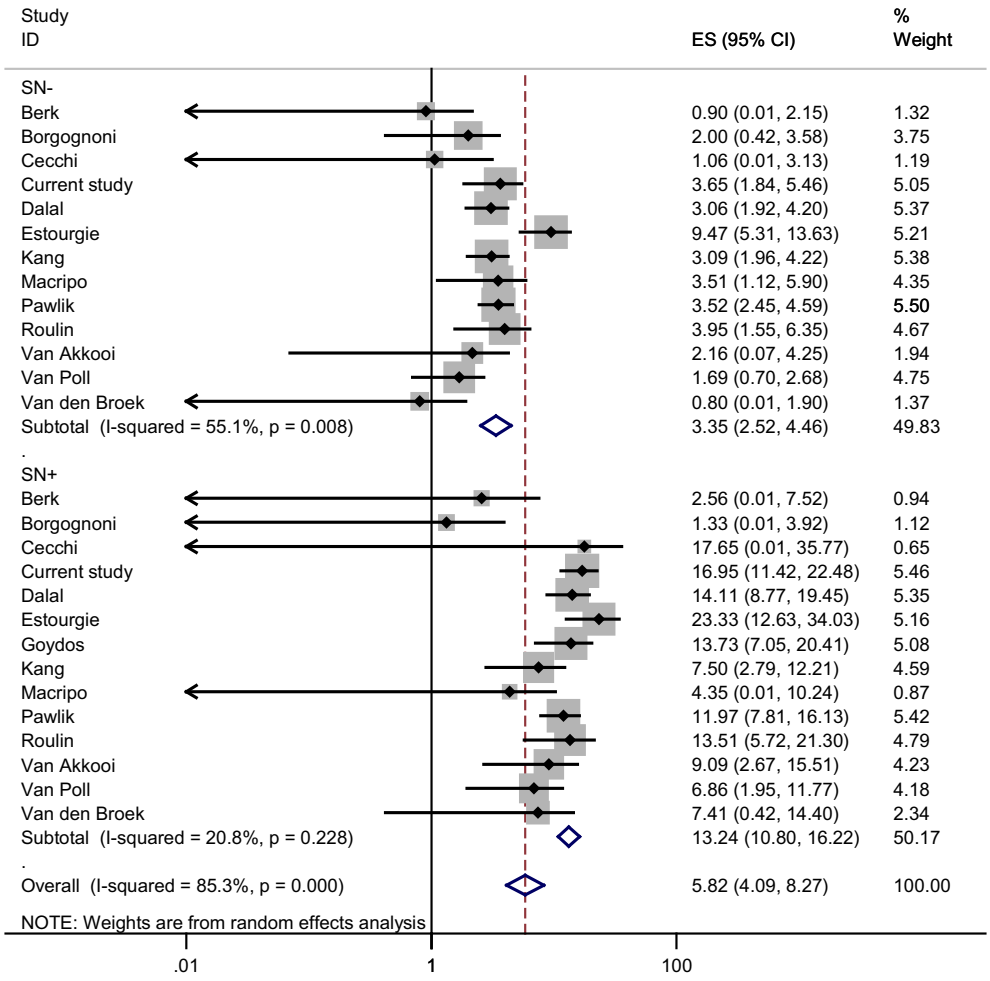

Fig. 2. Pooled percentage of ILM according to SLNB positive or negative result.

as ITM, SL and LR complicate comparisons among trials. Recently some authors have even abandoned the concept of a true local recurrence, merging ITM, SL and local recurrence into locoregional metastasis, leading to considerable data loss [57]. Also, data on mitosis index, Breslow thickness and ulceration status were inconsistent, thus complicating comparisons, necessitating interpreting the results with caution. In general, patients included in SLNB studies have less favorable primary tumor characteristics than patients who undergo WLE alone [58]. Moreover, before introduction of the SLNB technique, patients with less favorable tumor characteristics were to undergo ELND and would therefore not be included in WLE studies. These limitations may account for the difference between this review and the MSLT-I, a prospective study, in which no increase in ILM or local metastasis was reported between biopsy and observation groups (7.7 ± 1.0% and 8.4 ± 1.3%, respectively; $p = 0.38$). As we included WLE patients before introduction of SLNB our WLE population would differ from the MSLT-I population.

The percentage of ILM after DLND in our study is lower than expected. This may be due to the small sample size and also due to bias as we only included ILM as FR after DLND. Since these patients have aggressive disease, they may more often progress to distant metastasis instead of locoregional disease.

Summary

This review showed an increase in ILM of 1.5% after only performing a SLNB procedure (ILM 1.9% for WLE vs. 3.4% for SLNB−). Taking into account the patient groups traditionally included in WLE studies it is difficult to say whether this increase represents an actual increase in ILM recurrence or a selection bias.

The SLNB procedure is the most important prognostic tool in clinical practice, providing a survival benefit in selected SLNB+ patients undergoing CLND and potentially serving as a marker to identify patients for adjuvant therapy. Sentinel lymph node biopsy has been suspected of causing to increase intralymphatic metastasis by restricting lymph flow. This review demonstrates this increase, but this result has to be interpreted with caution due to possible selection bias. As the stasis hypothesis seems to be incorrect based on the data in this study, aggressive tumor characteristics are likely the cause of this increase. We therefore advocate performing SLNB procedures, but to proceed with caution, adhere to the guidelines and not extend the indication area.

Conflict of interest statement

The authors declare no conflict of interest.

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